A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Analgesic Efficacy of MNK-795 Controlled-Release Oxycodone/Acetaminophen Tablets (CR OC/APAP) in an Acute Pain Model

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Mallinckrodt Pharmaceuticals

Introduction

- Immediate-release (IR) oxycodone (OC) provides analgesia within an hour after administration; however, dosing every 4 to 6 hours is required to maintain analgesia over time[1,2]
- Oxycodone, an opioid analgesic, is commonly used in combination with acetaminophen (APAP) to manage moderate to severe acute pain[3]
  - The effects of treatment with combination therapy (eg, opioids combined with the centrally acting nonopioid analgesic APAP) are thought to be at least additive and may allow for the management of pain at a lower dose of each component, potentially reducing the risk of concentration-dependent adverse events[4-6]
- Formulations engineered to provide quick and sustained release may offer therapeutic benefit as well as reduce the pill burden[5,7]
- MNK-795 (CR OC/APAP) is a controlled-release (CR) combination OC/APAP analgesic, and is being designed to provide both fast onset of analgesia within 1 hour and sustained analgesia over the 12-hour dosing interval
  - CR OC/APAP tablets employ a dual-layer biphasic delivery mechanism that, when administered as a single dose (ie, 2 tablets), ensures the IR component delivers 3.75 mg OC/325 mg APAP and the extended-release component delivers 11.25 mg OC/325 mg APAP
  - Incorporates technology designed to provide tamper resistance and abuse deterrence
- In this pivotal clinical trial, CR OC/APAP was studied in an acute pain model in patients undergoing a first metatarsal bunionectomy
  - The bunionectomy model is a commonly used and accepted model of acute pain used for evaluation of new analgesics[8]

Objectives

- Evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain

Methods

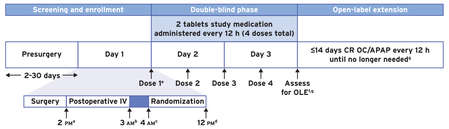
PATIENTS

- Patients undergoing unilateral, first metatarsal bunionectomy who reported at least moderate or severe pain intensity and numeric rating scale score of ≥4 (out of 10) between the hours of 4:00 AM and 12:00 PM (after cessation of intravenous popliteal nerve block) on the first postoperative day were eligible for the study

STUDY DESIGN

- This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study of CR OC/APAP (7.5 mg/325 mg) in patients with moderate to severe acute pain
  - The study consisted of a screening period of between 2 and 30 days before surgery, a randomized double-blind dosing phase of 2 days (48 hours) post procedure, and an optional ≤14 day open-label extension for qualified patients (**Figure 1**)

FIGURE 1: Study Design



[1]Surgery completed; [2]Nerve block stopped; [3]Earliest start for pain assessment and randomization; [4]Latest start for pain assessment and randomization; [5]Study medication administered within 30 minutes of randomization; [6]Patients assessed for participation in open-label extension within 48 to 52 hours of receiving first dose of study drug; [7]End-of-treatment evaluations performed within 3 days of receiving last dose of study drug; follow-up telephone call 7±2 days after receiving last dose of study drug (double-blind and open-label phases).

- Patients were randomized to receive a single dose of 2 tablets of CR OC/APAP (15 mg OC/650 mg APAP) or placebo administered every 12 hours (0, 12, 24, and 36 hours; 4 total doses) for 48 hours
  - Use of supplemental analgesia was permitted (ie, ibuprofen 400 mg up to 6 times per day [2400 mg/d]) during the double-blind (in both arms) and open-label phases of the study
- Exclusion criteria included any medical condition that might decrease adherence to study medication or alter the absorption, distribution, metabolism, or excretion of the study drug (eg, severe chronic diarrhea, chronic constipation, irritable bowel syndrome, or unexplained weight loss); gastric bypass surgery or gastric band; history of intolerance to short-term opioid use; and treatment with study drug or bunionectomy in previous 3 months

ASSESSMENTS

- Pain intensity was rated with an 11-item numerical rating scale (0 = no pain; 10 = the worst pain imaginable)
- The primary outcome measure was the summed pain intensity difference over the first 48 hours ($SPID_{48}$)
  - $SPID_{48}$ was calculated as the sum of time-weighted pain intensity difference (PID) scores over the first 48 hours (PID = [baseline pain intensity score] – [pain intensity score at time point of interest])
- Secondary outcome measures included pain intensity scores, PID associated with each pain intensity score, and SPID at multiple time points over 48 hours; total pain relief (TOTPAR) at multiple time points over the first 48 hours; and the time to perceptible, meaningful, and confirmed pain relief
  - To reduce the confounding effects of censored (unusable) pain scores due to use of supplemental analgesia (ie, ibuprofen), PID was estimated using multiple imputation techniques and 6-hour censoring, respectively
  - The double stopwatch method was used to determine time to onset of pain relief
- Global assessment of subject satisfaction was conducted during the study
- Safety and tolerability assessments were conducted throughout the double-blind and open-label phases of the study; adverse events were assessed at follow-up, and any significant measures were followed-up as medically indicated

Results

PATIENT POPULATION

- A total of 329 patients were enrolled and received ≥1 dose of study drug in the blinded-dosing phase of the study
  - 293 patients (89.1%) completed the double-blind phase of the study
- Efficacy analyses were performed on a modified intent-to-treat (mITT) population (N=303) randomized to treatment with either CR OC/APAP (n=150) or placebo (n=153)
  - Demographic and baseline characteristics of the mITT population were generally similar between groups (**Table 1**)

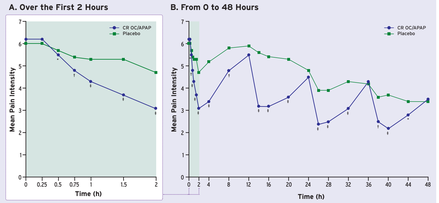
TABLE 1: Demographic and Baseline Characteristics (mITT Population)

Parameter	CR OC/APAP (n=150)	Placebo (n=153)
Age, y, mean (SD)	41.9 (13.1)	44.1 (14.0)
Sex, n (%)		
Male	19 (12.7)	26 (17.0)
Female	131 (87.3)	127 (83.0)
Race, n (%)		
White	85 (56.7)	95 (62.1)
Black	48 (32.0)	45 (29.4)
Asian	13 (8.7)	11 (7.2)
American Indian or Alaska Native	3 (2.0)	0
Native Hawaiian or other Pacific Islander	0	1 (0.7)
Other	1 (0.7)	1 (0.7)
Weight, kg, mean (SD)	70.3 (13.1)	72.2 (12.8)
Body mass index, kg/m^2, mean (SD)	25.6 (4.0)	26.4 (3.7)
Baseline pain intensity score, mean (SD)	6.2 (1.7)	6.0 (1.5)

EFFICACY

- As measured by the $SPID_{48}$ (the primary measure), pain reduction at 48 hours was greater in patients receiving CR OC/APAP versus placebo (mean [standard error (SE)], 114.9 [7.6] vs 66.9 [7.6], respectively; treatment difference of 48.0 [SE, 10.5]; $P<0.001$)
- Decrease in pain intensity scores over time is shown in **Figure 2**

FIGURE 2: Pain Intensity Scores Over Time Following Treatment With CR OC/APAP and Placebo



[1]$P<0.05$; [2]$P<0.001$; [3]$P<0.0001$.

- Mean PID for CR OC/APAP was numerically superior beginning at the earliest time point measured (15 min); statistical significance was reached 30 minutes after the first dose of study drug ($P<0.02$)
- Mean SPID over 0-4 (6.5), 0-12 (13.0), 0-24 (27.7), and 0-36 hours (39.7) were all statistically significant for CR OC/APAP versus placebo ($P<0.001$ for all comparisons)
- Mean TOTPAR over 0-4, 0-12, 0-24, 0-36, and 0-48 hours were all significantly greater for CR OC/APAP versus placebo (**Table 2**)

TABLE 2: Total Pain Relief Over 0-4, 0-12, 0-24, 0-36, and 0-48 Hours

TOTPAR Interval	CR OC/APAP (n=150)[1]	Placebo (n=153)[1]	Treatment Difference (95% CI)	*P* Value
0-4 h	6.8 (0.4)	3.4 (0.4)	3.4 (2.4-4.4)	<0.001
0-12 h	16.5 (0.9)	11.2 (0.8)	5.3 (2.9-7.7)	<0.001
0-24 h	38.4 (1.7)	26.8 (1.6)	11.6 (7.1-16.2)	<0.001
0-36 h	64.2 (2.5)	47.5 (2.5)	16.8 (9.8-23.8)	<0.001
0-48 h	91.3 (3.5)	70.9 (3.4)	20.5 (11.0-30.0)	<0.001

[1]Mean (SE).
CI=confidence interval.

- More patients receiving CR OC/APAP experienced perceptible, meaningful, and confirmed perceptible pain relief
- Median time to pain relief was significantly shorter for CR OC/APAP compared with placebo (**Table 3**)

Table 3: Median Time to Onset of Perceptible, Confirmed Perceptible, and Meaningful Pain Relief

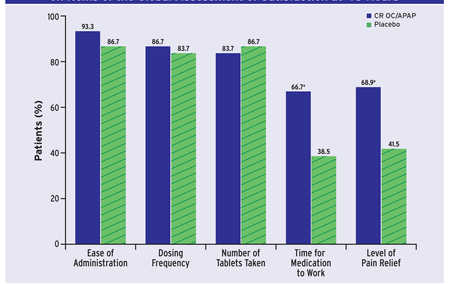
Time, min	CR OC/APAP (n=150)	Placebo (n=153)	*P* Value
To perceptible pain relief	33.56	43.63	0.002
To confirmed perceptible pain relief	47.95	NE	<0.001
To meaningful pain relief	92.25	NE	<0.001

NE=could not be estimated due to less than half the subjects experiencing confirmed or meaningful pain relief.

PATIENT SATISFACTION

- At the end of the double-blind phase, more patients indicated they were either "satisfied" or "very satisfied" with time taken for medication to work and level of pain relief by pain medication for CR OC/APAP compared with placebo (**Figure 3**)
- As would be expected, there were no differences between groups on ease of taking, frequency of taking, or amount of medication taken

FIGURE 3: Percentage of Patients "Satisfied" or "Very Satisfied" on Items of the Global Assessment of Satisfaction at 48 Hours



*$P<0.001$.

SAFETY AND TOLERABILITY

- Overall, during the blinded-dosing phase of the study, 37.7% of patients in the safety population (124/329) experienced a treatment-emergent adverse event (TEAE)
- The most common TEAEs reported during the blinded-dosing phase of the study are summarized in **Table 4**
  - As expected for this class of medication, a greater percentage of patients receiving CR OC/APAP reported nausea (30.7% vs 5.5%), dizziness (13.3% vs 1.2%), headache (9.6% vs 4.9%), skin and subcutaneous disorders (9.0% vs 4.3%), vomiting (9.0% vs 0%), and somnolence (3.6% vs 0.6%) compared with patients receiving placebo, respectively
  - Constipation was reported by a small percentage of patients receiving either CR OC/APAP or placebo (4.2% vs 3.1%, respectively)
- One patient in the group receiving CR OC/APAP reported a severe TEAE (headache), and no serious adverse events were reported during the blinded-dosing phase of the study

TABLE 4: Summary of Treatment-Emergent Adverse Events Occurring in >3% of Patients

Treatment-Emergent Adverse Event, n (%)	CR OC/APAP (n=166)	Placebo (n=163)	All Patients (N=329)
Any TEAE	89 (53.6)	35 (21.5)	124 (37.7)
Nausea	51 (30.7)	9 (5.5)	60 (18.2)
Dizziness	22 (13.3)	2 (1.2)	24 (7.3)
Headache	16 (9.6)	8 (4.9)	24 (7.3)
Skin and subcutaneous tissue disorders	15 (9.0)	7 (4.3)	22 (6.7)
Vomiting	15 (9.0)	0	15 (4.6)
Constipation	7 (4.2)	5 (3.1)	12 (3.6)
Somnolence	6 (3.6)	1 (0.6)	7 (2.1)

Conclusions

- CR OC/APAP was effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model
- Onset of pain relief was rapid and within 1 hour for CR OC/APAP as shown by the times to perceptible pain relief and confirmed perceptible pain relief compared to placebo
- CR OC/APAP administered as 2 tablets every 12 hours provided significant and sustained analgesia over the 48-hour testing period
- A greater proportion of subjects in the CR OC/APAP group compared with the placebo group were satisfied with analgesia at 48 hours and the time taken for pain medication to work
- The results support that CR OC/APAP is effective for patients with moderate to severe acute pain

References

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Disclosures

Dr. Singla received grants as a clinical investigator from Mallinckrodt Inc. Dr. Barrett, Ms. Sisk, Dr. Young, and Dr. Giuliani are employees of Mallinckrodt Inc. Dr. Kostenbader is a paid consultant to Mallinckrodt Inc.

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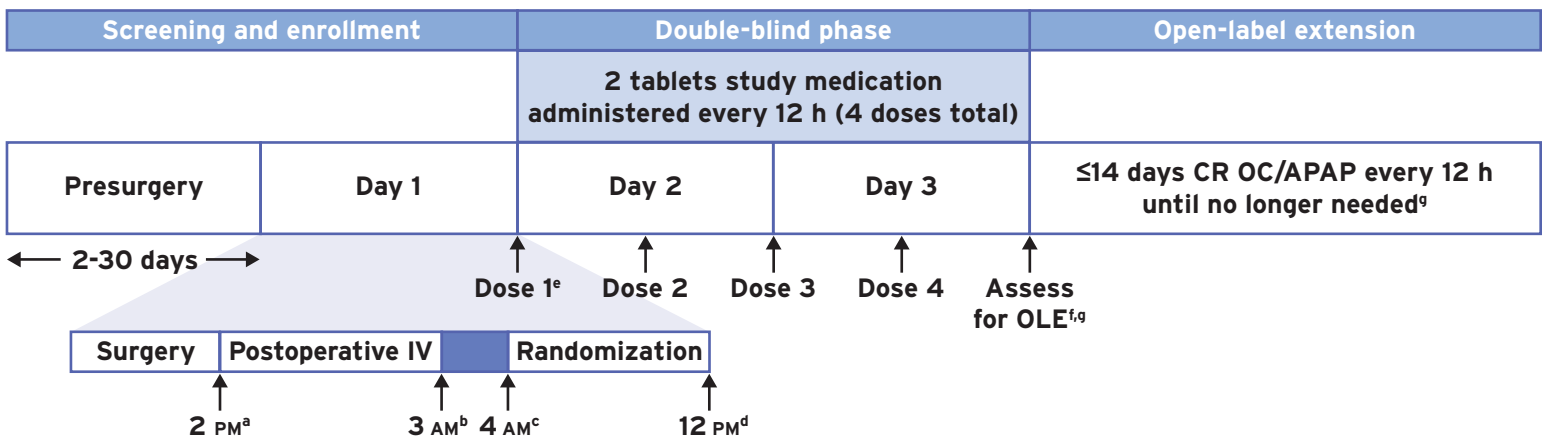

[a]Surgery completed; [b]Nerve block stopped; [c]Earliest start for pain assessment and randomization; [d]Latest start for pain assessment and randomization; [e]Study medication administered within 30 minutes of randomization; [f]Patients assessed for participation in open-label extension within 48 to 52 hours of receiving first dose of study drug; [g]End-of-treatment evaluations performed within 3 days of receiving last dose of study drug; follow-up telephone call 7±2 days after receiving last dose of study drug (double-blind and open-label phases).

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- A total of 329 patients were enrolled and received ≥1 dose of study drug in the blinded-dosing phase of the study
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- Efficacy analyses were performed on a modified intent-to-treat (mITT) population (N=303) randomized to treatment with either CR OC/APAP (n=150) or placebo (n=153)
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Weight, kg, mean (SD)	70.3 (13.1)	72.2 (12.8)
Body mass index, kg/m^2, mean (SD)	25.6 (4.0)	26.4 (3.7)
Baseline pain intensity score, mean (SD)	6.2 (1.7)	6.0 (1.5)

EFFICACY

- As measured by the $SPID_{48}$ (the primary measure), pain reduction at 48 hours was greater in patients receiving CR OC/APAP versus placebo (mean [standard error (SE)], 114.9 [7.6] vs 66.9 [7.6], respectively; treatment difference of 48.0 [SE, 10.5]; *P*<0.001)
- Decrease in pain intensity scores over time is shown in **Figure 2**

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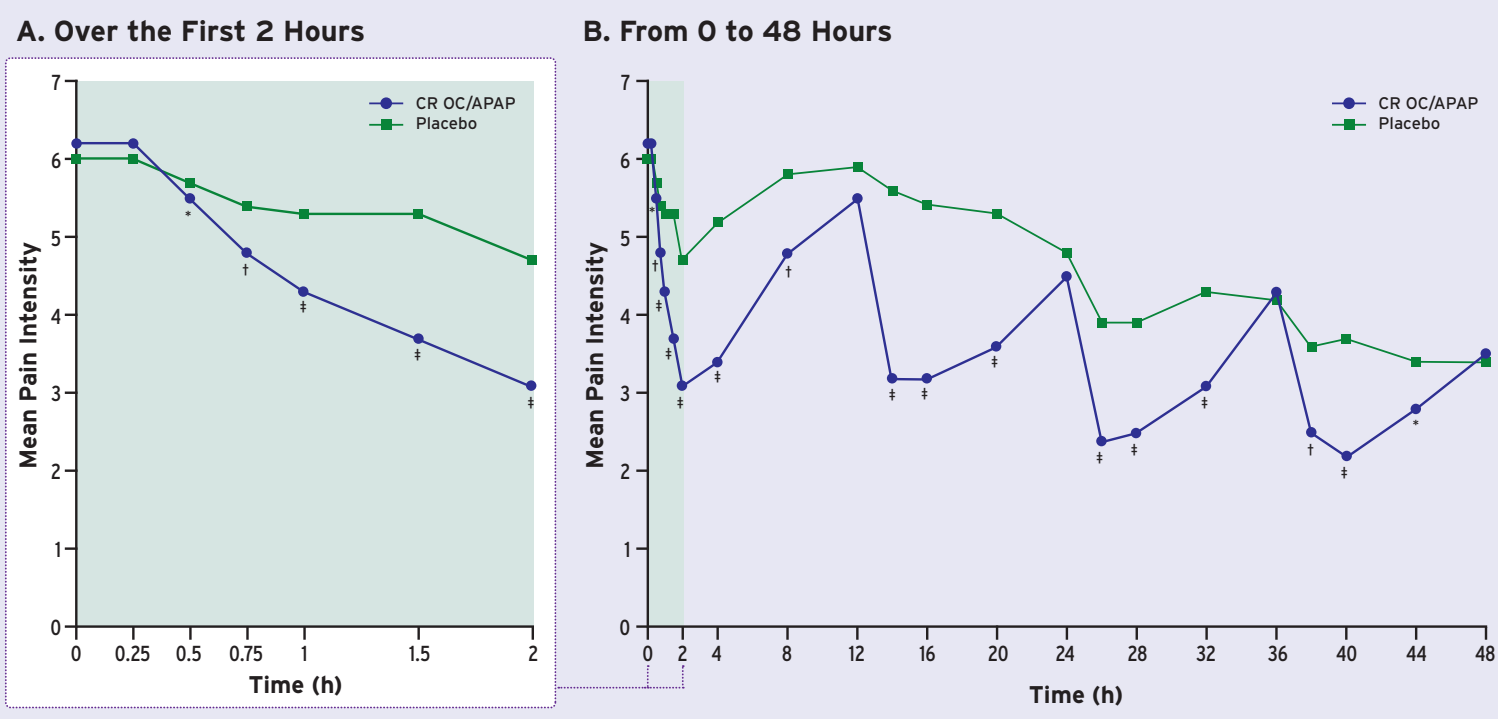

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TOTPAR Interval	CR OC/APAP (n=150)[a]	Placebo (n=153)[a]	Treatment Difference (95% CI)	*P* Value
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0–36 h	64.2 (2.5)	47.5 (2.5)	16.8 (9.8–23.8)	<0.001
0–48 h	91.3 (3.5)	70.9 (3.4)	20.5 (11.0–30.0)	<0.001

[a]Mean (SE).
CI=confidence interval.

- More patients receiving CR OC/APAP experienced perceptible, meaningful, and confirmed perceptible pain relief
- Median time to pain relief was significantly shorter for CR OC/APAP compared with placebo (**Table 3**)

Table 3: Median Time to Onset of Perceptible, Confirmed Perceptible, and Meaningful Pain Relief

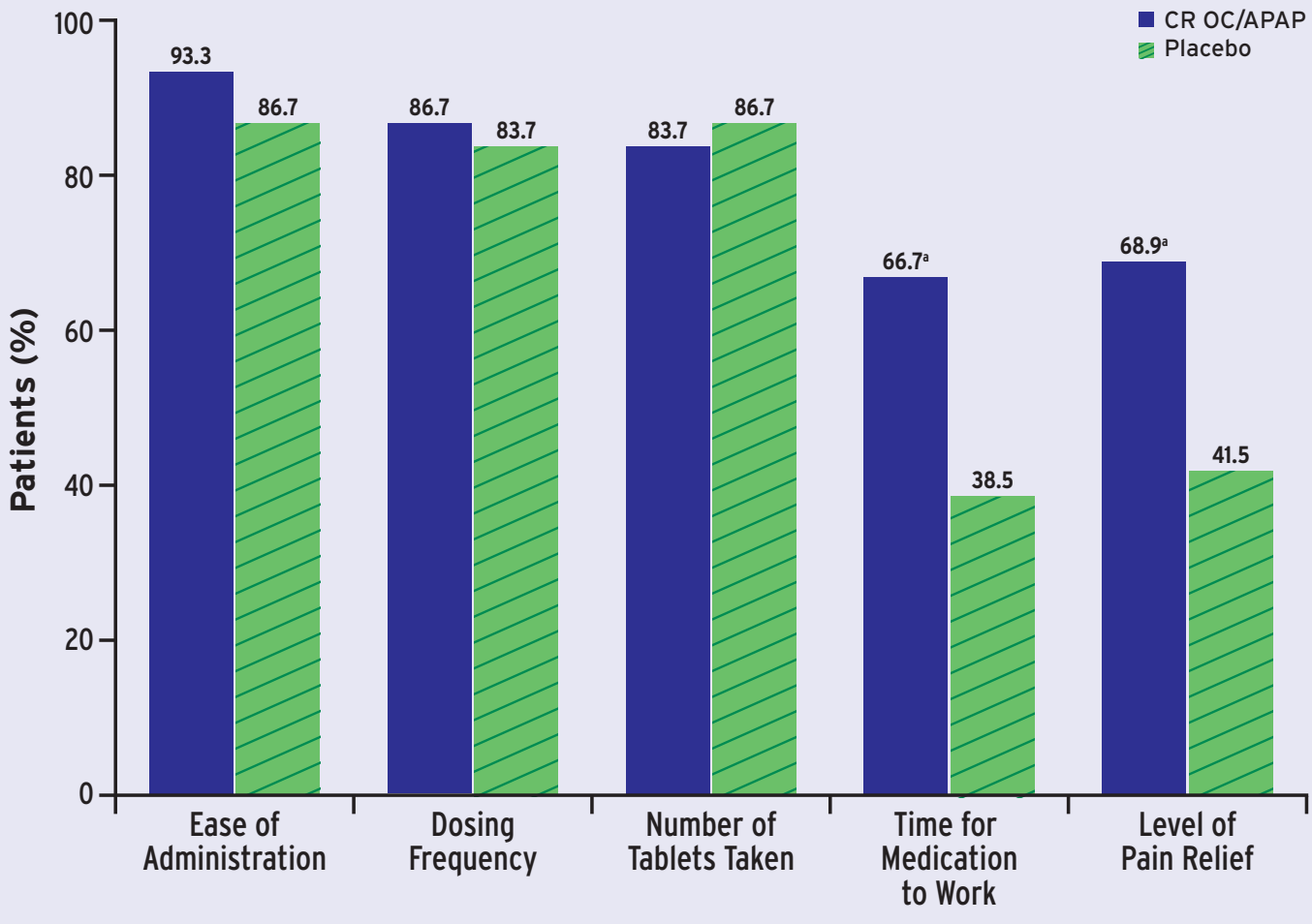
Time, min	CR OC/APAP (n=150)	Placebo (n=153)	*P* Value
To perceptible pain relief	33.56	43.63	0.002
To confirmed perceptible pain relief	47.95	NE	<0.001
To meaningful pain relief	92.25	NE	<0.001

NE=could not be estimated due to less than half the subjects experiencing confirmed or meaningful pain relief.

PATIENT SATISFACTION

- At the end of the double-blind phase, more patients indicated they were either "satisfied" or "very satisfied" with time taken for medication to work and level of pain relief by pain medication for CR OC/APAP compared with placebo (**Figure 3**)
- As would be expected, there were no differences between groups on ease of taking, frequency of taking, or amount of medication taken

FIGURE 3: Percentage of Patients "Satisfied" or "Very Satisfied" on Items of the Global Assessment of Satisfaction at 48 Hours



[a]*P*<0.001.

SAFETY AND TOLERABILITY

- Overall, during the blinded-dosing phase of the study, 37.7% of patients in the safety population (124/329) experienced a treatment-emergent adverse event (TEAE)
- The most common TEAEs reported during the blinded-dosing phase of the study are summarized in **Table 4**
  - As expected for this class of medication, a greater percentage of patients receiving CR OC/APAP reported nausea (30.7% vs 5.5%), dizziness (13.3% vs 1.2%), headache (9.6% vs 4.9%), skin and subcutaneous disorders (9.0% vs 4.3%), vomiting (9.0% vs 0%), and somnolence (3.6% vs 0.6%) compared with patients receiving placebo, respectively
  - Constipation was reported by a small percentage of patients receiving either CR OC/APAP or placebo (4.2% vs 3.1%, respectively)
- One patient in the group receiving CR OC/APAP reported a severe TEAE (headache), and no serious adverse events were reported during the blinded-dosing phase of the study

TABLE 4: Summary of Treatment-Emergent Adverse Events Occurring in >3% of Patients

Treatment-Emergent Adverse Event, n (%)	CR OC/APAP (n=166)	Placebo (n=163)	All Patients (N=329)
Any TEAE	89 (53.6)	35 (21.5)	124 (37.7)
Nausea	51 (30.7)	9 (5.5)	60 (18.2)
Dizziness	22 (13.3)	2 (1.2)	24 (7.3)
Headache	16 (9.6)	8 (4.9)	24 (7.3)
Skin and subcutaneous tissue disorders	15 (9.0)	7 (4.3)	22 (6.7)
Vomiting	15 (9.0)	0	15 (4.6)
Constipation	7 (4.2)	5 (3.1)	12 (3.6)
Somnolence	6 (3.6)	1 (0.6)	7 (2.1)

Conclusions

- CR OC/APAP was effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model
- Onset of pain relief was rapid and within 1 hour for CR OC/APAP as shown by the times to perceptible pain relief and confirmed perceptible pain relief compared to placebo
- CR OC/APAP administered as 2 tablets every 12 hours provided significant and sustained analgesia over the 48-hour testing period
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References

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